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Identification of Sex, Strain, and Entourage Effects in the Behavioral and Physiological Response to Cannabinoids

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Recent policy changes will increase the prevalence of cannabis use in the US. Marked variation among individual humans in both the acute and chronic response to cannabis suggests that genetic factors play a role in initial behavioral response and sustained use, and persistent effects. However, the precise genetic and biochemical mechanisms mediating adverse health consequences to cannabis and its constituent components are unknown and this represents a critical barrier to progress in leveraging the therapeutic potential of cannabis and identifying individuals at risk for adverse side effects. Accordingly, our group has initiated a project to study the effects of genetics on behavioral and physiological responses following acute and chronic exposure to two main components of cannabis, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), in C57BL/6J (B6), DBA/2J (D2) and their recombinant inbred BXD progeny. We have developed a phenotyping pipeline that measures hypothermic, analgesic, and motor response phenotypes during acute and chronic exposure to cannabinoid mixtures (THC and THC + CBD). We report significant and heritable strain, sex, and CBD effects on THC response between the parents of the BXDs—C57BL/6J and DBA/2J—and identify heritable variation in the physiological response to THC using a subset of the BXD cohort. We propose that physiological and behavioral responses to cannabinoids are driven by genetic variation in effector proteins that regulate cannabinoid 1 receptor (CB1) signal transduction, termination of signaling, and trafficking. Future directions include the identification of the genes moderating individual differences in cannabinoid response using forward genetic mapping in the BXD panel.